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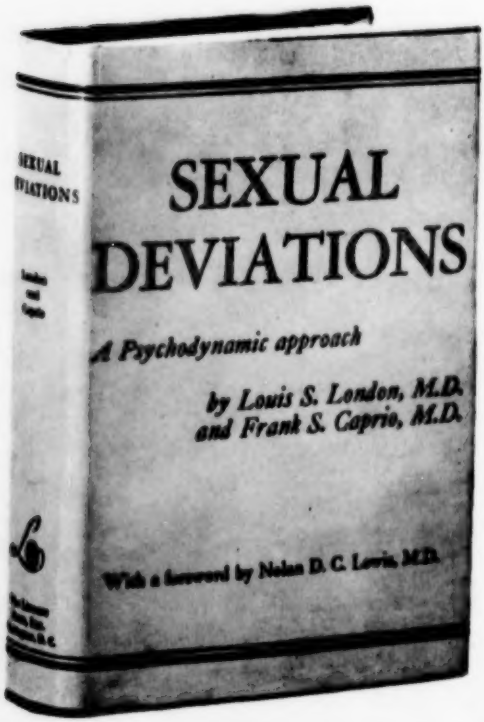
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Thirty Years of Mercurial Diuretics

A Review of Their History and Present Status

ALFRED VOGL, M.D.*

On the 16th of October, 1919, the era of the mercurial diuretics began with the unexpected effect of an injection of novasurol.[1-13] The introduction of these drugs has, in the words of Willius and Dry[2], the historians of the heart, "completely revolutionized the treatment of congestive heart failure and has proved to be one of the greatest therapeutic innovations of all time." On the thirtieth anniversary of this event, it may be appropriate to review briefly the history of this discovery and the development of our knowledge and of the use of these drugs.

Mercury in the form of an inorganic compound, mercurous chloride (calomel), had been used as a diuretic since the days of Paracelsus;[3] it was an important ingredient of the famous diuretic Guy's Hospital pills and was re-introduced by Jendrassik[4] who described its action on water and chloride excretion in 1886. Calomel, however, was unreliable in its action and never became very popular because of its cathartic and frequent toxic side effects.

It was the use of the *organic* mercurials as diuretic agents that began on October 16, 1919, in postwar Vienna. A 21-year-old girl with congenital syphilis had been admitted to Dr. Paul Saxl's ward at the Wenckebach Clinic for antisyphilitic treatment. I happened to be the clinical clerk in charge of the case at that time. It was through a series of coincidences that I used an ampule of novasurol which, by a lucky chance, we had received as a free sample just that morning. (Novasurol-merbaphen had been introduced as a mild parenteral antisyphilitic drug about two years before.[5]) The patient was emaciated, weighed 71 pounds and showed no trace of edema. She received an injection of novasurol on alternate days (Table 1). After each injection her urinary output was recorded as greatly increased for 24 hours while it became very scanty on the days without injection.[1] When this occurred for the fourth time, I felt sure that these waves of diuresis were not coincidental and had the vague notion that they might be the result of some shock-like curative effect of the mercury on the syphilitic kidney. I reported these observations to Dr. Saxl, the attending physician. Impressed by the action of novasurol on urinary output in the absence of edema, it seemed reasonable to try it in cases in which stimulation of diuresis would be desirable. Still in the belief that the diuretic effect of the

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drug resulted from its antisyphilitic action, we selected for this purpose a few patients with syphilitic heart disease who were in congestive failure and severely edematous. In each case an amazing diuresis was obtained. Finally, we ventured to give it, as a last resort, to a critically ill boy with rheumatic heart disease in far-advanced congestive failure. The effect was equally dramatic. Only then did we realize that we were dealing with a drug that possessed a powerful diuretic action entirely independent of its antisyphilitic properties.

TABLE 1

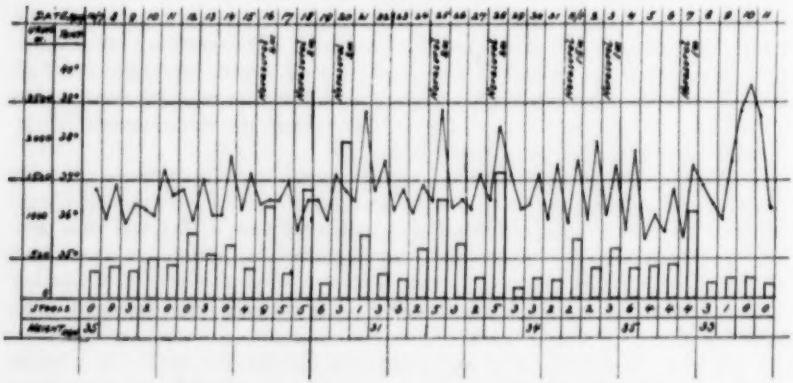

Chart of Urinary output of J.M., a non-edematous girl, on whom, in October 1919, the diuretic action of novasurol was discovered.

The report of these observations[6] immediately aroused great interest and was followed by a multitude of publications from all countries up to the present. But to-day, after three decades of prodigious work on mercurial diuretics and despite their extensive use in medical practice, their exact standing as therapeutic agents is still somewhat controversial.

The studies of Saxl and Heilig[7] established the fact that the diuretic effect of novasurol consisted in a massive excretion of chloride together with a large output of water. They regarded anasarca, particularly cardiac edema, as the prime indication, but included other conditions such as cirrhosis of the liver and serosal or synovial effusions of chronic inflammatory nature. Soon afterwards it was recommended also as a weight-reducing agent in the treatment of obesity.[8] All the early workers, basing their studies on the current concepts of renal function, looked to the extrarenal tissues as the primary site of the diuretic action[7,9,10] but the evidence in favor of such action remained unconvincing. The well-known picture of mercurial poisoning from overdosage was the only form of toxicity known

to occur. Recognized contraindications to the use of mercury of any kind were acute and chronic glomerulonephritis, for fear of further renal damage, and, empirically, cachexia and severe anemia.[7]

This, briefly, was the status of the mercurial diuretics in 1920. In the following 30 years the development of the mercurials concerned their practical use as diuretic agents as well as the theory of their action.

The clarification of their mode of action progressed step by step, beginning with experimental evidence that the mercurials act directly on the kidney[11] even if it is isolated[12,13] or transplanted into a non-mercurialized host.[14] At the same time the evidence adduced earlier in favor of primary extrarenal action was invalidated when later investigators, using improved methods, were unable to corroborate the occurrence of transient hydremia prior to the onset of diuresis.[15,20]

The exact mode of action of the mercurials on the kidney became understandable with the advancement of renal physiology. The work of Schmitz,[16] Hermann,[21] Blumgart,[17] and others has demonstrated convincingly that the diuretic action of the organic mercurials represents an early reversible toxic effect on the tubular epithelium by the slightly dissociated mercury ion. This action impairs tubular reabsorption of water and chloride[22] from the glomerular filtrate and in this way leads to an increase in the volume of urine as long as the inhibition of tubular activity lasts. During this period fluid is shifted from the extracellular compartment to the plasma to compensate for the lost plasma fluid. The net result is diminution of tissue edema, absorption of transudates in serosal cavities and decrease of the circulating blood volume, partly due to the initial fluid loss and, probably to a greater part, due to a redistribution of blood in capillary spaces previously unavailable because of edema.

This process is essentially identical in edematous and non-edematous individuals.[23] The statement encountered occasionally that mercurials are ineffectual in normal individuals, is erroneously based on 24-hour weight controls. If, however, the first 6 hours after the injection are used for comparison, an increase in diuresis up to threefold can be seen even in normal persons[17] (Table 2). But unlike the edematous individual, the normal per-

TABLE 2

ACTION OF MERCURIALS IN NORMAL PERSONS[17]

	S. D.	*Days*	*1*	*2*	*3*	*4* (*mercurial*)	*5*	
		1st 7 hrs.	640	290	660	1440	590	
		24 hrs.	1340	940	1330	1990	1250	
S. A.	*Days*	*1*	*2*	*3* (*mercurial*)	*4*	*5*	*6*	*7* (*mercurial*)	*8*
	First 7 hrs.	660	800	1120	670	800	890	1000	680
	24 hrs.	1800	1700	1700	1620	1880	1880	1880	1630

son who has no stores of excess fluid will promptly retain water and salt from the ingested food during the remainder of the day and, 24 hours after the injection, his weight may have returned to that of the preceding day.

As far as the toxic manifestations accompanying mercurial therapy are concerned, our concept had to be changed fundamentally. It has become apparent that a clear distinction must be made between true toxicity arising from the mercurial compound itself and syndromes related to the effects of intensified diuresis and not to the diuretic agent itself.[24]

Among the true toxic manifestations we have to differentiate again those typical of heavy metal poisoning from manifestations which are related to hypersensitivity of the individual to either the mercury ion itself or to the specific organic compound. Mercurialism as the result of accumulation of mercury in the system is probably avoidable in most cases with proper care. The amount of mercury in the tissues at any given time is, of course, proportionate to the rate of absorption and excretion and is therefore negligible with the newer mercurial diuretics provided their administration is followed by an adequate diuresis. Seventy to 85% of the mercury is excreted in the urine within 24 hours if the diuresis exceeds 2,000 cc.[25,26] The rate of urinary excretion of the mercury is the decisive element in the controversy about the advisability of *daily* mercurial injection.[27] There is obviously no need to repeat injections daily if the diuretic effect is satisfactory and an interval of 48 hours will insure against accumulation of mercury in the system. If, however, the mercurial fails to produce diuresis, a considerable portion of the injected mercury is retained in the body and it obviously becomes dangerous to attempt forced diuresis by daily (or larger) doses. The disregard of these principles has led to mercurial poisoning with stomatitis, colitis and even fatal anuria from tubular necrosis.[28,29,30] The use of BAL can probably change the grave outlook in some cases if treatment is promptly instituted. However, if cumulation is avoided mercurials can be given, and have been given regularly for years, with continuous effectiveness and without any demonstrable harm.[31,32] There is no evidence indicating a development of tolerance to mercurials.

Direct myocardial toxicity has been reported in some cases following intravenous injection, and is apparently due to idiosyncrasy since in animal experiments similar effects could be obtained only with inordinately large doses.[33,37,40] The toxic symptoms observed are altered cardiac irritability or conductivity, from intraventricular block, the appearance of premature ventricular contractions and paroxysmal ventricular tachycardia to fatal ventricular fibrillation.[22,35,38] Other manifestations of hypersensitivity are more common but are very rarely encountered with the *first* administration of a mercurial. They have, however, the tendency to increase in intensity with repetition of the drug[39] and may change from mild reactions such as chills, fever or vomiting to more serious ones such as oppression, dyspnea, anxiety, perspiration, pallor or faintness, and finally reach alarming proportions, with cardiac irregularities, syncope and death.[41] This serious type of reaction has not been reported to follow intramuscular injection. Minor

reactions should never be ignored and changing from the intravenous to the intramuscular or subcutaneous route may prove life-saving. If reactions follow intramuscular injections, a change from one organic mercurial to a different one may often abolish the reaction.

A syndrome that follows profuse diuresis and has in the past been confused with mercurial toxicity, is now recognized as being the result of excessive dehydration and salt depletion.[42 44] It can be described as resembling heat prostration and may exhibit all its symptoms from lassitude, headache and muscle cramps to delirium, azotemia and coma. This complication can usually be prevented by avoiding excessive diuresis and watching the electrolyte balance.[45] Another reason why sudden profuse diuresis should be avoided in elderly, bed-ridden males is the occasional occurrence of complete urinary retention as an unexpected sequel[46] and occasionally as the first manifestation of prostatic hypertrophy.

One important complication of mercurial diuresis which completely escaped the European investigators is the phenomenon of "redigitalization." Considerable amounts of digitalis in the edema fluid of digitalized patients were demonstrated by Miller and Smith (1931)[47] and again by Schnitker and Levine (1937)[48] who also observed the clinical effects of the mobilization of the digitalis depots on the heart. These observations solved the mystery of the occurrence of headache, nausea, vomiting, bradycardia, bigeminus rhythm and other arrhythmias subsequent to intensive mercurial diuresis. Even fatal ventricular tachycardia and fibrillation have been seen under these circumstances. Can such accidents be prevented now that their mechanism is fully understood? Discontinuing digitalis for several days, as has been suggested for very edematous patients prior to a mercurial injection, will hardly reduce the digitalis stores sufficiently, even if the condition of the patient were to allow such a step. Preliminary paracentesis of effusions is advisable and will remove some of the drug. Beyond these precautions, it is imperative to initiate diuresis in a patient who is fully digitalized and severely edematous as slowly as possible to avoid sudden flooding of the system with an unpredictable amount of digitalis. Quinidine given prophylactically for 48 hours under such circumstances may conceivably decrease myocardial irritability. Redigitalization and its dangers may be considered as an argument in favor of starting mercurial diuretics in edematous patients prior to, or simultaneously with, digitalization. Although it seems true that diuresis is more profuse after digitalization, the rapid subjective relief and the avoided risk of redigitalization are advantages that readily compensate for smaller initial diuresis.

The original organic mercurial novasurol (merbaphen) was soon replaced by improved compounds. Salyrgan (mersalyl) proved less toxic because of more prompt and more complete excretion of the mercury. The introduction of novurit (mercuzanthin) and similar compounds containing a small quantity of theophylline[49] represented further progress; this combination prevents necrosis at the site of injection, the mercurial is absorbed

and excreted faster and thereby attains a brief but effective peak of topical concentration in the renal tubular epithelium.[50,52] These compounds were highly satisfactory and have been used almost exclusively for close to 25 years. The only objections against their use were the occasional allergic reactions when given intravenously and poor absorption and painful infiltration when given intramuscularly into edematous tissue. The newly introduced thiomerin, a compound containing a mercaptide group in place of theophylline[53] obviates these drawbacks as it can be given subcutaneously with minimal local irritation,[54] and animal experiments have demonstrated its extremely low toxicity[55] (apparently due to the presence of a sulfhydryl group).[44] If further experience confirms the preliminary impression that it is just as effective as the older compounds, it may develop into the diuretic of choice. In edematous patients whose veins are inaccessible, the intrapleural or intraperitoneal route should be remembered as a feasible mode of administration if effusions are present in one of these cavities.[55,56]

Preparations for oral and rectal use, although greatly improved since the earliest attempts,[57] are still far from perfect, rather irregular in absorption and therefore unpredictable in diuretic action and toxic potentialities; frequently they are also locally irritating.[58,61] The synthesis of an effective oral mercurial diuretic reasonably free of these limitations would be extremely desirable.

Contraindications to the use of mercurial diuretics have changed little from the earliest days; they include colitis and poor oral hygiene. Cachexia and severe anemia are no longer emphasized, probably because edema in these conditions has been recognized as being due to hypoproteinemia and is no longer regarded as an object of diuretic treatment. Renal insufficiency is, by general consent, regarded as the only serious contraindication,[62] especially that in acute diffuse glomerulonephritis since edema is uncommon in other forms of renal insufficiency. The use of mercurials in this condition is prohibited not primarily for fear of injuring the diseased kidneys directly, but because lack of concentrating power impairs the diuretic effect; this in turn causes poor excretion and prolonged retention of the mercury with all the dangers of mercurial poisoning, including that of toxic nephrosis. In genuine nephrosis the concentrating power is not impaired and mercurials are often used for symptomatic relief. A warning must, however, be sounded: among patients suffering from nephrosis the number of fatal reactions reported following intravenous injection of a mercurial is, for reasons unknown, disturbingly high.[43] Incidentally, azotemia, if occurring in advanced congestive heart failure, is not a contraindication. It may disappear with the loss of edema and improved circulation.

The factors which contribute to the subjective and objective improvement that follows adequate diuresis in heart failure have gradually become more clearly defined. Some factors are obvious, such as the reduction of weight and the concomitant diminution of the burden for the heart on locomotion; the abolition of tension and stiffness that greatly hamper the

motility of the edematous patient; the relief from abdominal distention, indigestion and epigastric pressure caused by a congested liver and ascites and the alleviation of respiratory distress caused by pleural effusions and ascites. Decrease of pulmonary congestion could be plainly demonstrated by a prompt and significant rise in vital capacity[61,64] which, at least in part, explains the rapid relief from respiratory distress by copious diuresis. Diminution of the circulating blood volume with decrease of the venous pressure was suggested by the often striking disappearance of neck vein engorgement and has been definitely demonstrated by a number of workers;[18,20,23,64,67] this may be the factor chiefly responsible for the improvement of circulation by promoting diuresis. The role played by the decrease in peripheral resistance that results from loss of edema for the improvement of circulation may be considerable, but is difficult to appreciate. No proof has, however, been produced for the assumption that reduction of edema of the myocardium itself may play any part in the restoration of myocardial efficiency.[63]

The main point of controversy up to this day is the exact range of indications for mercurial diuretics. In accordance with the earliest recommendations,[7] there is general agreement that they should be used for cardiac edema if other measures fail to abolish it. But whether they are indicated in cardiac edema prior to treatment with bed rest and digitalis, in congestive heart failure without edema, in cardiac conditions not associated with failure, and finally in non-cardiac conditions with edema or serosal effusions, the answers to all these questions unfortunately are still controversial or at least appear not sufficiently clarified in the minds of many practitioners. And as a consequence of contradictory statements by experienced cardiologists,[43,74] attitudes may be encountered which range from the employment of a mercurial, for fear of its toxicity, as an ultimum refugium only, to its free and indiscriminate use as a cure-all for heart disease and edema of any kind.

In an attempt to delineate these indications more definitely it may be mentioned that, among the indications propounded by early writers, inflammatory exudates as well as obesity have been generally discarded.

On the other hand, congestive heart failure in the absence of any palpable edema has been added as an important indication and emphasized by numerous competent observers[25,31,68,70] but the value of mercurials for this purpose is still not sufficiently appreciated in medical practice. Right heart failure usually responds so well to mercurials that the alleviation of hepatic and portal congestion is promptly felt. In such cases the size of the liver can be used as an index of the effect of an injection and of the necessity of repeating it. The most gratifying indication for mercurial diuretics is, no doubt, passive pulmonary congestion[71] whether due to left ventricular failure, chronic or occasionally acute, or to mechanical obstruction (mitral stenosis). In the latter condition in which, particularly with regular cardiac rhythm, decrease in cardiac output is not a major factor, the mercurials are unquestionably more effective than digitalis. In minor

degrees of pulmonary congestion manifesting themselves only by orthopnea or intractable nocturnal cough, a mercurial gives the patient not only prompt relief and sleep but acts as a therapeutic test which establishes the need for digitalis. Incidentally, the effects of a mercurial diuretic on dyspnea and physical findings may also be used in the sometimes difficult differentiation of bronchial asthma from pulmonary congestion.

The preventive use of mercurials for attacks of paroxysmal nocturnal dyspnea[72,73] recurring in spite of digitalization is as satisfactory as it is little used: a daily weight record is necessary as a guide to indicate the need for an injection whenever the weight either rises sharply or the established "dry weight"* of the patient is gradually exceeded by 2 to 3 pounds. Such a weight rise notoriously presages another attack of cardiac asthma and can usually be averted by timely diuresis. As Gold has indicated,[27] the maintenance of a steady body weight can serve as a guide for a "maintenance dose" of mercurial diuretics, allowing, of course, for a change in the nutritional status.

All these observations have been widely confirmed and, whenever there is need for rapid relief, whether because of the patient's distress or of the necessity to shorten his invalidism, there is apparently no sound contraindication to the use of a mercurial initially before digitalization is accomplished. This course may often make rapid emergency digitalization avoidable. There is, however, no evidence available to indicate that mercurials are a substitute for digitalis although there are a few conditions, such as mitral stenosis with pulmonary congestion and regular cardiac rhythm, decompensated cor pulmonale, and particularly active carditis with congestive failure, in which treatment with mercurials alone seems superior to that with digitalis. I admit some skepticism regarding the extension of the indications of mercurials to the use in some cases with cardiac arrhythmias, anginal syndrome and hypertension.[74] It seems impossible to rule out the presence of mild congestive failure among the cases of successful treatment reported.

Even with strict indication and adherence to the rules advocated above patients with congestive failure are encountered who respond poorly or not at all to mercurial diuretics. The number of apparently refractory cases is, however, diminishing steadily with increasing comprehension of the diversity of causes for such failures. The most obvious cause for failure of an intramuscular mercurial injection, slow absorption with subsequent poor concentration in the kidneys, has been greatly overcome by avoiding injections into edematous tissue and by the use of the newer mercurial compounds containing theophylline[50,51] or mercaptide,[52,54] especially since the latter (thiomerin) can be given subcutaneously into any edema-free parts of the body.

With the increasing popularity of low-salt or salt-free diets in the treatment of congestive heart failure, and the prolonged use of mercurial diur-

*This term is used here to denote the patient's optimum weight at which he is *free* of symptoms and signs of congestive failure and not his minimum weight after maximal dehydration.

etics, ineffectiveness is encountered more frequently after a series of injections. If one attempts to overcome this deadlock by a more vigorous use of the mercurials the results are not improved, but the danger of mercurial poisoning is increased. Years passed before it was realized that lowering of plasma sodium and chloride resulting from a combination of low salt intake and induced massive salt loss may be the cause of failure of mercurials at this stage.[45,75,76] Lowering of the plasma electrolytes below a certain level is apparently resisted by vital regulatory mechanisms which are able to overcome the action of mercurials and prevent a further loss, retaining at the same time a corresponding amount of water. The depletion in chlorides can be averted by ammonium chloride medication.[75] However, in a case refractory to mercurials, only plasma sodium and chloride determinations can clarify the situation and, if low values are found, sodium chloride must be supplied either orally, or, more effectively, by injection of hypertonic saline until electrolyte balance has been restored. With a sufficient amount of sodium chloride again available in the plasma, satisfactory diuretic action can be expected.

The failure of mercurials in far-advanced cardiac insufficiency is, of course, their most serious limitation. Admittedly this failure is difficult to reconcile with our present concepts of their mode of action. Reduction of glomerular filtrations to an extent at which inhibited reabsorption would no longer lead to a significant urinary output, is difficult to visualize. For prognostic purposes the cases of "failure" of a mercurial, i.e., the patients who show no weight loss after 24 hours, may be divided into two groups. The first group represents failure in a clinical but not in a physiologic sense. Some increase in urinary output does take place during the first few hours after the injection but oliguria during the remaining hours of the day comsates for the earlier fluid loss. In these cases congestive failure appears so severe that the transient diuretic effect is quickly cancelled by the rate at which water and salt pour back into the tissues. We have learned from experience that this type of "failure" is not hopeless and that combination with other therapeutic agents may still change the picture. The second group, however, consists of patients without even a transitory increase in diuresis. These are probably all terminal and their glomerular filtration rates have presumably dropped to almost zero. Restitution of renal blood flow at this stage of congestive failure is hardly to be expected. In cases of the first group, vigorous efforts to overcome the deadlock are indicated. Full digitalization is, of course, the first prerequisite. Simultaneous use of diuretics with different sites of action often leads not only to a summation but to a potentiation of their effects.

Of the diuretic adjuvants, ammonium chloride has become by far the most popular.[26,77–80] It does not only supply the chloride necessary for the maintenance of diuresis but also acts as an acidifying agent. Acidification of the tissue fluids changes their osmotic pressure, alters the water-binding properties of the proteins and thus apparently initiates removal of extracellular body water. Taking ammonium chloride in doses of 5 to 8 Gm. on

TABLE 3

HYPERTENSIVE AND ARTERIOSCLEROTIC HEART DISEASE WITH AURICULAR FIBRILLATION, CONGESTIVE HEART FAILURE. (R. H., 61, MALE)

Date	*Weight*	*Medication*	*Remarks*
8/29	190		In progressive failure for 3 mos., fully digitalized, taking amm. chlor. regularly; received frequent Hg. injections.
8/30	191½	mercupurin 2 cc. i.v.	
8/31	190		Scanty diuresis.
9/ 1	190½		
9/ 2	193	mercupurin 2 cc. i.v.	No improvement
9/ 3	192		Hydrothorax aspirated (1200 cc.).
9/ 4	193		
9/ 5	193		
9/ 6	192	mercupurin 2 cc. i.v.	
9/ 7	191		Condition unchanged
9/ 8	193	mercupurin 2 cc. i.v.	
9/ 9	192½		
9/10	195		Urine very scanty. Severe dyspnea and cyanosis.
9/11	196	mercupurin 2 cc. + aminoph. 0.48 i.v. aminophylline 0.48 i.v.	Good diuresis.
9/12	191	aminophylline 0.48 i.v. (2x)	Less dyspneic
9/13	189	mercupurin 2 cc. + aminophylline 0.48 i.v. aminophylline 0.48 i.v.	Profuse diuresis.
9/14	184	aminophylline 0.48 i.v. (2x)	Marked improvement.
9/15	182	aminophylline 0.48 i v. (2x)	Continued diuresis.
9/16	181½	mercupurin 2 cc. + aminophylline 0.48 i.v.	Profuse diuresis.
9/17	176	aminophylline supp. 0.36 (2x)	
9/18	176½	aminophylline supp. 0.36 (2x)	No dyspnea at rest; hydrothorax, sacral and abdominal wall edema disappeared, 2+ of lower extremities.
9/19	176	mercupurin 2 cc. + aminophylline 0.48 i.v.	
9/20	172	aminophylline supp. 0.36 (2x)	
9/21	170		
9/22	171	mercupurin 2 cc. i.v.	
9/23	166½		
9/24	167	aminophylline supp. 0.36 (2x)	Patient lost 30 lbs. in 14 days, is ambulatory, sleeps well. Liver 1½ f. below CM, 1 + ankle edema.
9/25	166		

TABLE 4

SYPHILITIC HEART DISEASE, AORTIC INSUFFICIENCY, SEVERE CONGESTIVE FAILURE. (A. J., 52, FEMALE)

Date	*Weight*	*Medication*	*Remarks*
7/ 7	121		Admitted because of lack of response to digitalis and mercurials.
7/ 8	122¼	mercuhydrin 2 cc. i.m.	No improvement (severe dyspnea, neck vein engorgement, 3+ leg edema, large liver).
7/ 9	122		
7/10			
7/11		mercuhydrin 1 cc. i.m.	No improvement. Rice diet.
7/12			
7/13	120	mercuhydrin 2 cc. i.m.	No improvement.
7/14			
7/15	121	mercuhydrin 2 cc. i.m.	No improvement.
7/16			
7/17			
7/18			
7/19			No improvement.
7/20		mercuhydrin 2 cc. i.v. aminophylline 0.48 Gm. i.v.	
7/21	119		Edema slightly decreased.
7/22		mercuhydrin 2 cc. i.v. aminophylline 0.48 Gm. i.v.	
7/23	116		
7/24			
7/25		mercuhydrin 2 cc. i.v. aminophylline 0.48 Gm. i.v.	Improved.
7/26	114¾		
7/27			
7/28			
7/29		mercuhydrin 2 cc. i.v. aminophylline 0.48 Gm. i.v.	
7/30	113½		Edema greatly decreased.
7/31			
8/ 1		mercuhydrin 2 cc. i.v. aminophylline 0.48 Gm. i.v.	
8/2	112		Minimal ankle edema.

the day prior to, and the day of the injection of a mercurial appears to be the most economic mode of administration of this drug. One of the most efficacious combinations of diuretics, often with spectacular results, is the concomitant use of aminophylline and a mercurial. It has, in our hands, repeatedly turned a state of apparently intractable terminal cardiac failure into one of reasonable comfort. A rather dependable schedule for this purpose begins with an intravenous injection of a mixture of 2 cc. of a mercurial and 0.48 of aminophylline which is followed by another aminophylline injection the same day and two more, evenly spaced, on the second day. This two-day schedule may be repeated until the goal has been achieved (Tables 3 and 4). It may be the added action of aminophylline

upon glomerular filtration,[16,67] upon the respiratory centers[81,82] or upon venous pressure[83] that accounts for the revival of diuresis.

Another drug, decholin, alone a weak and unreliable diuretic, can occasionally increase mercurial diuresis considerably.[86–87] This is true particularly in cases with predominantly hepatic congestion or with cirrhosis of the liver. It is also given mixed with the mercurial in one intravenous injection. It is possible that it acts by way of influencing the capacity of the liver to control water metabolism.[88] In a refractory case the combined use of all these adjuvants is often gratifying. It is the combination of diuretic agents rather than the employment of larger and more frequent mercurial injections that is advisable in refractory cases. Record diuretic outputs ("superdiuresis"[89]), however, are never desirable and lead to the ill effects of rapid dehydration already mentioned.

The anti-diuretic action which sedatives, particularly opiates, exhibit in some individuals should never be forgotten. It affects water as well as chloride excretion.[90] Its mechanism has been experimentally analyzed.[91] Sedation should not be sacrificed but the obstacle to diuresis involved in its use should be overcome by judicious timing. In chronic failure the ideal time to give a mercurial diuretic is early in the morning. By nightfall, when a sedative is often indicated, the effect of the diuretic will have spent itself. In acute left ventricular failure the problem becomes more difficult: morphine must be given as an emergency measure, at the same time the flooding of the lungs calls for a diuretic. Two to four hours after the onset of the attack the paroxysmal dyspnea will either have subsided or the anti-diuretic action of morphine will have worn off.[90] If a mercurial is given at this point it is no longer counteracted by the sedative and may avert a relapse of cardiac asthma or, in protracted cases, the perpetuation of, or the development into, frank pulmonary edema.

Looking back at the work of the past thirty years we must gratefully acknowledge the tremendous amount of energy which investigators throughout the world have devoted to the problem of mercurial diuresis. They have succeeded in greatly clarifying many questions involved and have helped to place the indications and contraindications for mercurial diuretics from a purely empirical start onto a sound scientific foundation. But it may take another thirty years before unanimity as to the range of clinical indications will be achieved and the exact place of the mercurial diuretics in medical practice will finally be established.

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Muscle Spasm and Paralysis in the Diagnosis of Acute Poliomyelitis

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The systemic symptoms of acute poliomyelitis, while consistently present, are of no decisive diagnostic significance. Malaise, headache and anorexia are common in all acute infections. The red throat, instead of being a diagnostic aid, is often misleading in furnishing an all too ready explanation beyond which the physician need look for the real nature of the disease.

How can the temperature curve be used as an important sign in confirming or excluding poliomyelitis in the acute stage? The usual temperature curve is well illustrated by the three paralytic and three non-paralytic cases shown in Plate I. Of the paralytic cases (Figures 1, 2 and 5, Plate I), the last was definitely the most severe. Whereas the first two (Figures 1 and 2, Plate I) showed normal temperatures on the fifth day of the disease, the last (Figure 5, Plate I) showed unbroken fever until the eighth day. Two days after showing normal temperature, the first patient complained of more pain in the back and developed a secondary rise in temperature which usually means an extension of the disease and generally does not occur after the first ten days. In this case the pain soon subsided and the temperature again returned to normal (on the eighth day of the disease).

The first of the three paralytic patients whose temperature charts are shown (Figures 3, 4 and 6, Plate I), a very severe case, showed a normal temperature on the fourth day of the disease, and no significant fever after that; the second of these showed a normal temperature when admitted to the hospital on the sixth day of the disease, after which time the temperature rose and failed to return to normal again until the ninth day of the disease. Figure 6, Plate I shows the temperature changes in one of the cases which ended fatally. This patient, a 12-year-old boy, walked into the hospital on the second day of the disease complaining of headache and stiffness of the neck, back, and hamstrings. Paralysis set in and progressed daily, involving all four extremities and, on the eleventh day, all of the muscles of respiration. At that point the boy was placed in a respirator where he remained until his death four days later. The continued elevation of temperature shown on his chart corresponds with the progress of the disease and is noteworthy.

The spinal fluid findings, upon which there is a general tendency among clinicians to rely for the final clue, are also unreliable. Too much reliance upon spinal fluid findings in our earlier work resulted in failure to diagnose 50 to 70% of cases of poliomyelitis in the early stage and misdiagnosis as poliomyelitis of a number of other conditions. Our previously reported figures[1] on the careful analyses of 95 samples of fluid taken from as many

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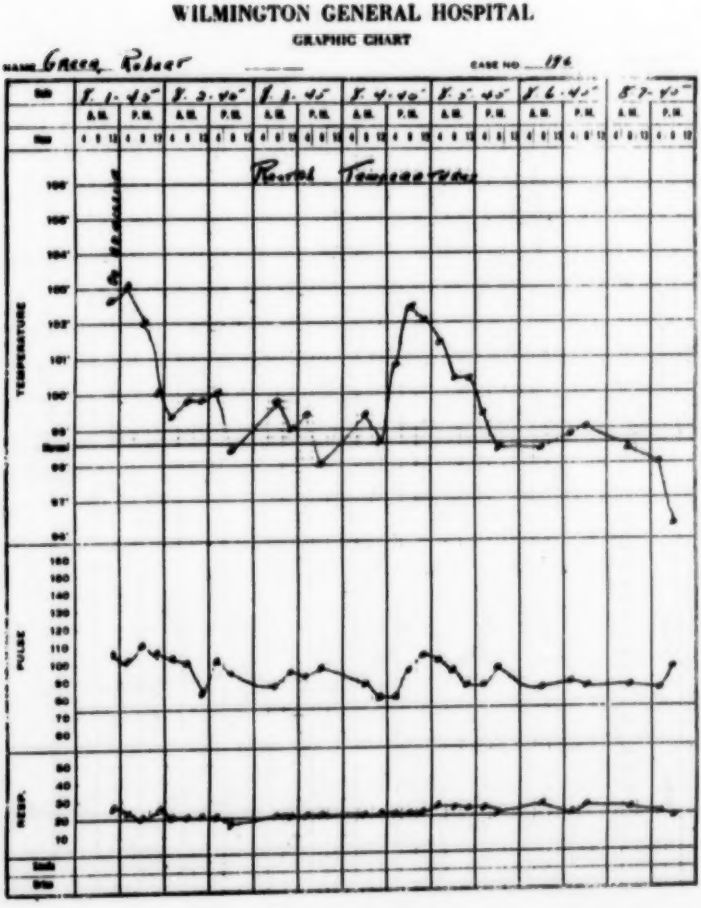

FIG. 1—Non-paralytic

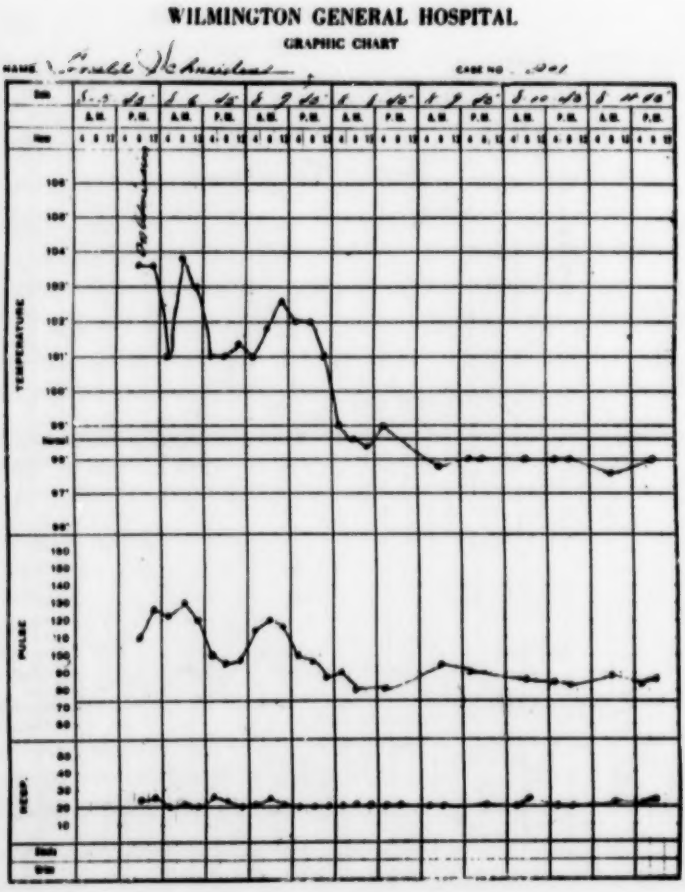

FIG. 2—Non-paralytic

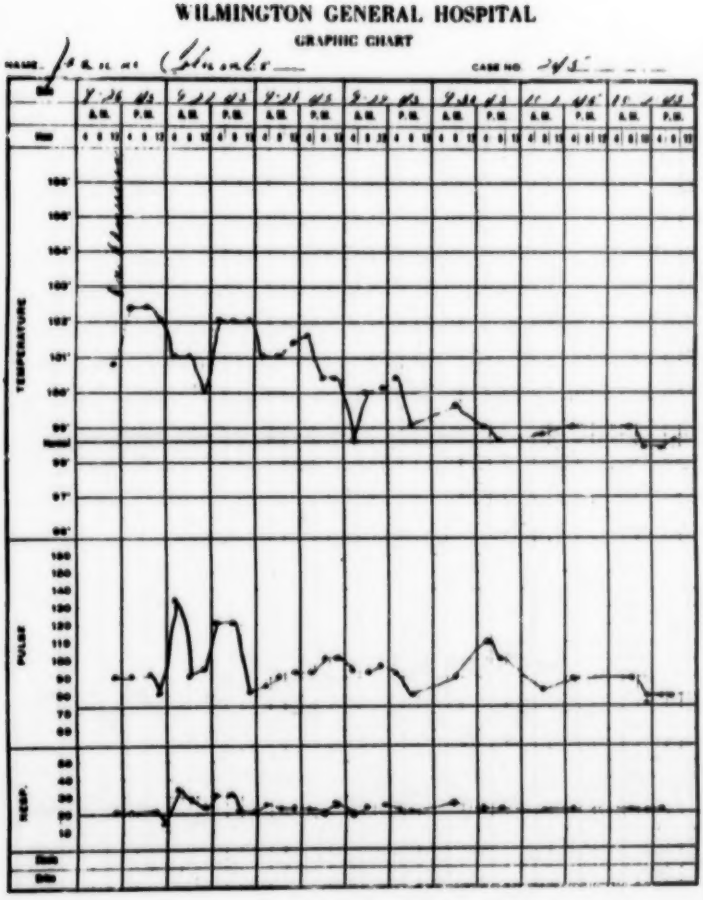

FIG. 3—Severe paralytic

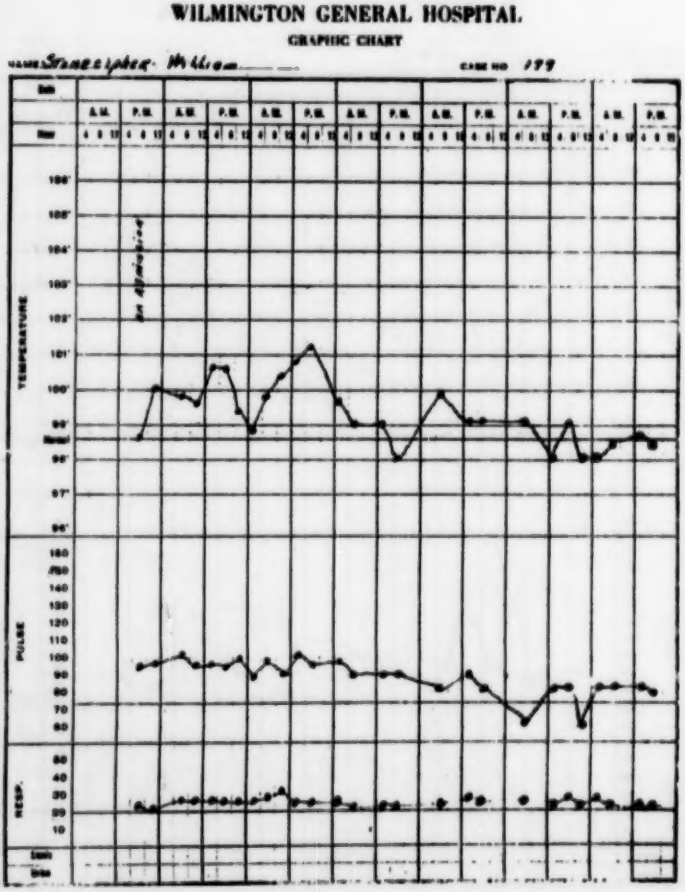

FIG. 4—Patient with complete paralysis of both lower extremities

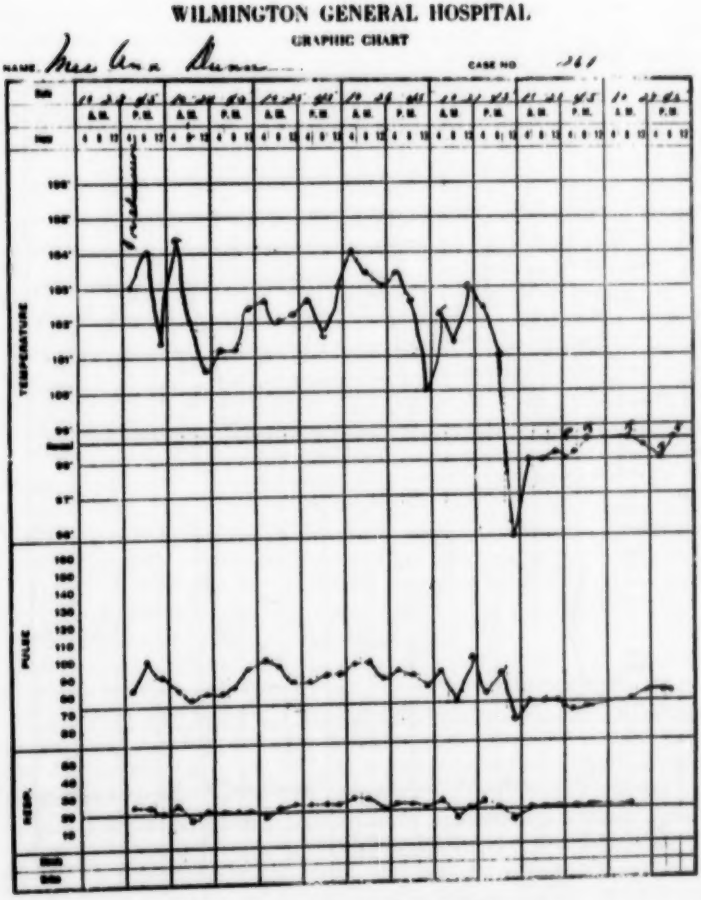

FIG. 5—Severe non-paralytic

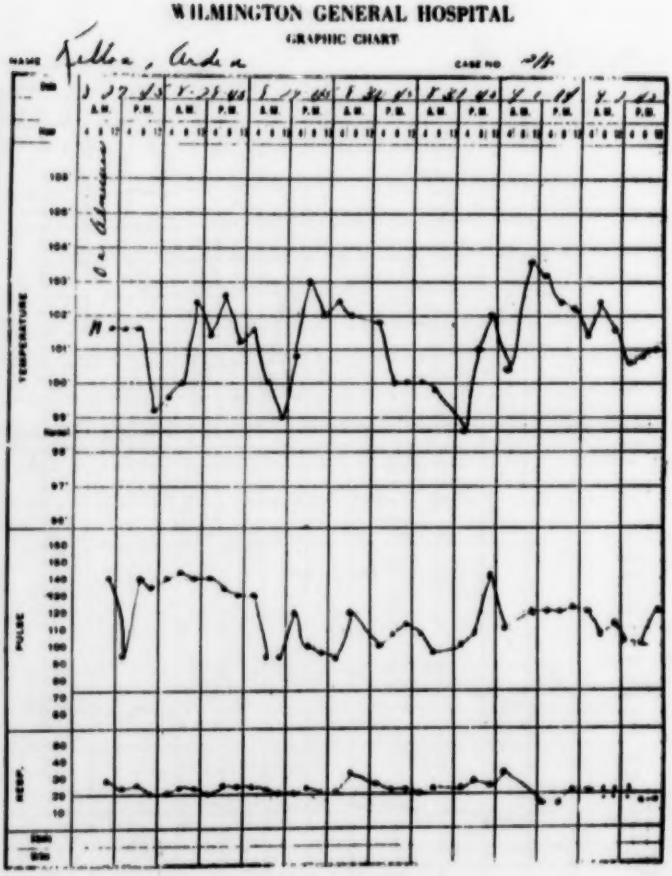

FIG. 6—Patient with progressive paralysis involving all extremities and chest muscles. Expired in respirator

patients (49 paralytics and 46 non-paralytics) during the acute stage of the disease give indisputable proof that a normal spinal fluid cell count cannot exclude a diagnosis of poliomyelitis.**

Since positive globulin reactions occurred often in spinal fluids with increased cell counts, and higher normal amounts of protein were usually correlated with increases in both globulin and the cell count, their diagnostic value is even more restricted than that of the spinal fluid cell counts. Blood analyses, from the standpoint of positive findings, have likewise proved of little assistance in the diagnosis of poliomyelitis.

At this point, it might be helpful to list certain signs and symptoms which usually exclude poliomyelitis.*** The following may be noted: (1) rash of any kind; (2) swollen glands; (3) convulsions; (4) purulent spinal fluid; (5) extreme drowsiness without muscle spasm or bulbar paralysis; (6) hemorrhagic or xanthochromic spinal fluid; (7) positive blood or spinal fluid serologic changes; (8) sensory changes such as anesthesia to heat, cold or pain; (9) eye ground changes; (10) localized joint changes (pain, swelling); (11) slow onset; (12) prolonged fever without paralysis; (13) jaundice; (14) bleeding gums or purpuric spots.

The procedure we have found most valuable for diagnosis of acute poliomyelitis in the early or febrile stage (i. e., in the first five to seven days), and by which a high percentage of wrong diagnoses may be avoided, is to follow the symptoms and signs presented by the muscle condition as originally described by Pohl.[2] The teaching that, because the virus attacks the anterior horn cells, flaccid paralysis has to be present before the diagnosis can be made, has not been borne out by our experience. Practically every acute poliomyelitis patient presents muscle spasm and every paralytic patient presents incoordination, weakness, and paralysis of the muscles in addition to a severe degree of muscle spasm. Spasm of various muscle groups is amply demonstrated in the accompanying photographs of acute poliomyelitis patients (Plates II and III).

In this diagnostic approach the physician must be alert to the muscle signs present in acute poliomyelitis as follows: (1) muscle spasm (muscles short, hypertonic, and painful); (2) stretched muscles; (3) incoordination of muscle action (i. e., other muscles trying to perform movements normally assigned to the affected muscles); (4) nerve-muscle dissociation ("mental alienation"), apparently paralyzed muscles which eventually recover completely; (5) muscle weakness or imbalance; (6) muscle paralysis; (7) leg shortening due to muscle spasm; (8) fasciculation and fibrillation.

Clearly, a knowledge of the individual muscles is essential before one can isolate those affected and determine the extent of their involvement. Through the investigation of muscle function one can trace the pathologic factors to the cranial nerves to the spinal cord segment where the anterior

**Fifty-three (55.8%) of the 95 spinal fluid specimens showed increased cell counts; of these 33 were from paralytic cases and 20 from non-paralytic. Forty-two (44.2%) of the specimens analyzed showed a cell count within normal limits, i. e., less than 10 cells; of these 26 were from non-paralytic patients and 16 from paralytics.

***One should keep in mind that it is possible to have two diseases at the same time.

PLATE 2

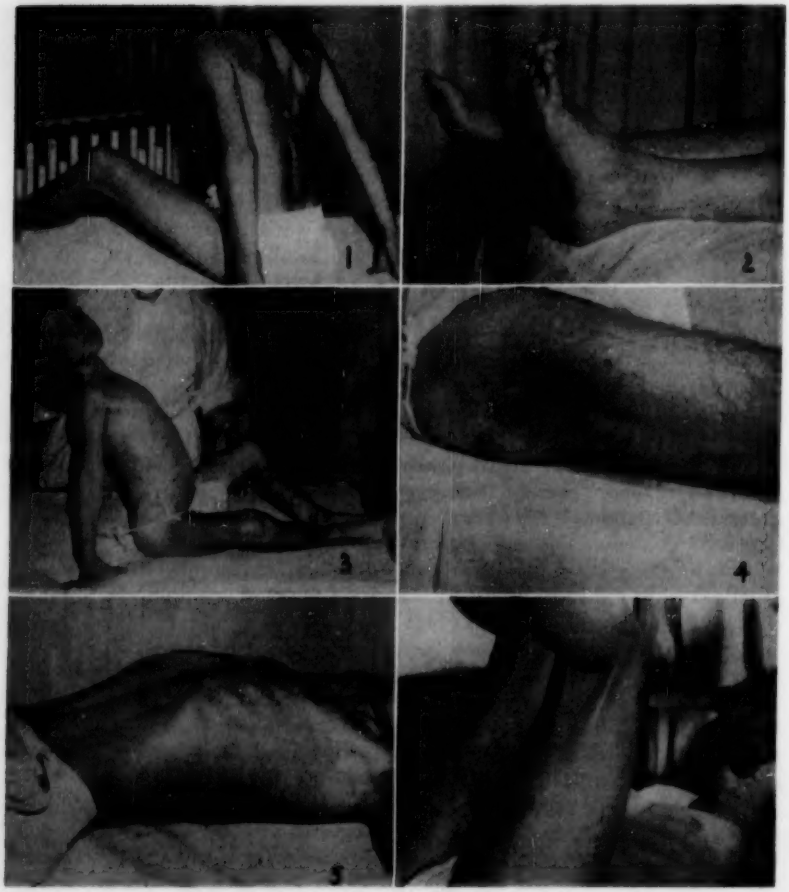

FIG. 1—Spasm of neck, paravertebral and hamstring muscles

FIG. 2—Spasm of left quadratus lumborum muscle causing shortening of left lower extremity

FIG. 3—Typical position due to spasm of neck and back

FIG. 4—Spasm of tensor fascia lata muscle and gluteus maximus causing tension of iliotibial band

FIG. 5—Lordosis with forward tilting of pelvis

FIG. 6—Spasm of hamstrings

PLATE 3

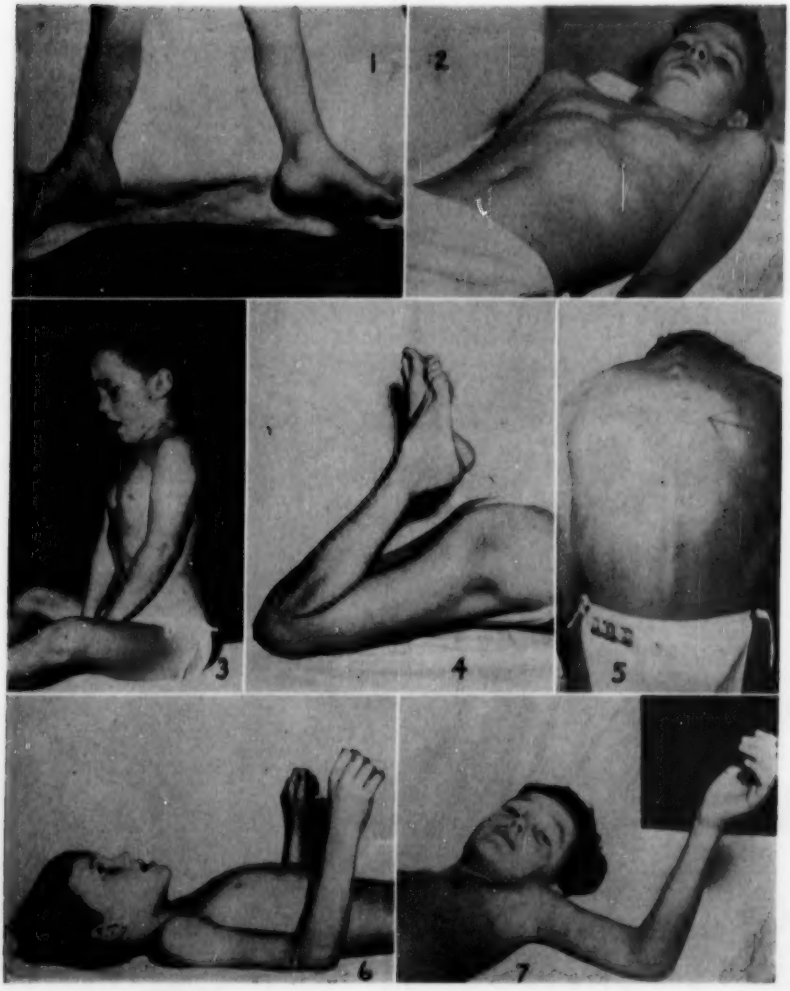

FIG. 1—Spasm and paralysis in gastroc-soleus muscles

FIG. 2—Spasm in pectorals, cupping of shoulders

FIG. 3—Limited flexion of neck and back; spasm of hamstrings

FIG. 4—Spasm of quadriceps femoris muscles

FIG. 5—Flat area of lower dorsal spine normally seen in older children and adults

FIG. 6—Bilateral spasm of brachialis and brachioradialis, keeping forearms in pronation

FIG. 7—Spasm of left brachialis and flaccid paralysis of triceps and extensors of fingers

PLATE 4

FIG. 1—Paralysis of left facial nerve. Unable to close eye

FIG. 2—Paralysis of right abdominal muscle with herniation

FIG. 3—Paralysis of left sternomastoid muscle

FIG. 4—Paralysis of outer hamstring (biceps femoris muscle). Note contraction of inner hamstrings

FIG. 5—Paralysis of intercostals and left diaphragm; chest is in state of inspiration. Left shoulder is weak. Spasm of left pectorals

FIG. 6—Paralysis of right anterior and posterior tibial muscles. Note contraction of right peroneals and atrophy of right leg

PLATE 5

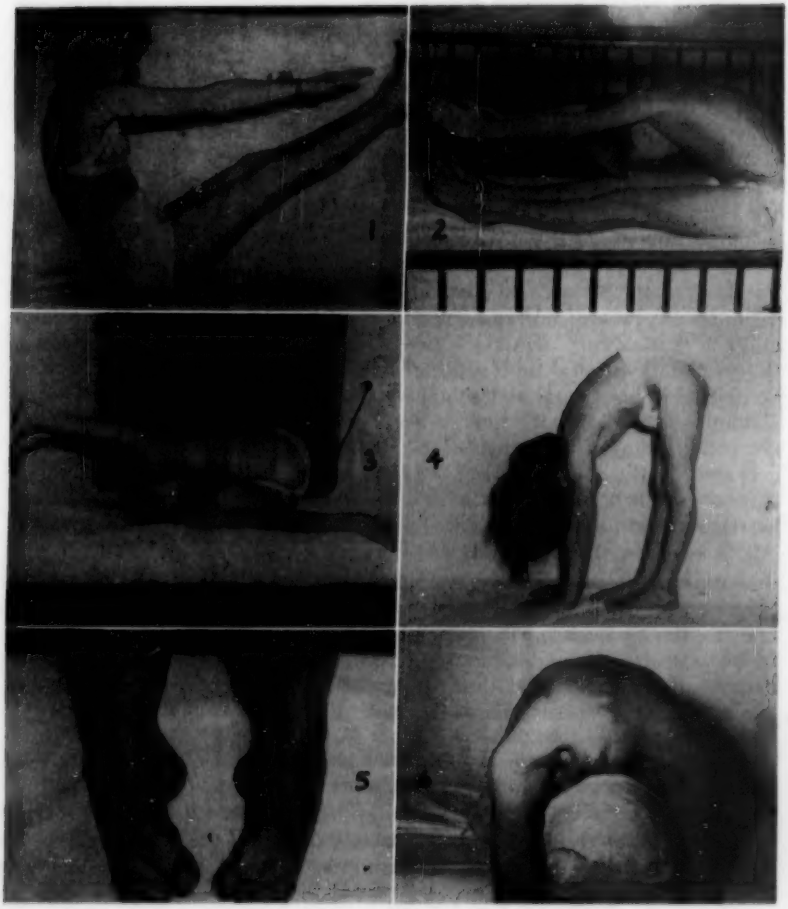

FIG. 1—Normal hip flexors and abdominals
FIG. 2—Relaxed neck, back and hamstrings
FIG. 3—Normal relaxation at back and lower extremities
FIG. 4—Normal relaxation, figure 8, Plate II
FIG. 5—Normal anterior tibials
FIG. 6—Relaxed spine. Note normal curvature

horn cells are involved in cases of spasm, weakness or paralysis or where the posterior sensory ganglia with their posterior horn cells are involved in cases of hyperesthesia.

The distribution of a nerve into several muscles explains the otherwise peculiar distribution of muscle spasm, weakness or paralysis in poliomyelitis (Plate IV). For example, when the upper extremity is paralyzed one can always expect spasm or paralysis of the diaphragm on the same side since the phrenic nerve gets its nerve supply from the third, fourth, and fifth cervical roots. Likewise when the entire deltoid muscle is involved, one may also expect paralysis of the latissimus and teres major muscles because of their common innervation through the posterior cord of the brachial plexus. A very common paralysis simultaneously involves the short head of the biceps femoris, gluteus medius and anterior tibial muscles which are supplied by the second, fourth, and fifth lumbar nerves and the first sacral. Spasm and paralysis of the gastroc-soleus group (supplied by the fifth lumbar and first two sacral nerves) and paralysis of ilio psoas muscles (supplied by the first four lumbar nerves) are likewise common. Paralysis of the anterior tibial muscle was associated with that of the abdominals in three of our cases (nerve supply the fourth and fifth lumbar and the first sacral). On the other hand, one may often see paralysis of the external, internal and transverse abdominal muscles and attendant herniation of the lateral abdominal wall, without involvement of the rectus abdominal muscles which have a nerve supply quite distinct from that of the other group of abdominals. Similarly, the sternomastoid muscle, innervated by the spinal accessory nerve, may be paralyzed while the upper trapezius, which receives an additional nerve supply from the third and fourth cervicals, may be only in severe spasm.

It is evident that the affected muscles must be isolated and rated as soon as the acute spasm is over so that the exact involvement of the patient's muscles may be known. It is also highly important for the physician to instruct the technician with regard to the muscles or muscle groups which require stretching reeducation and coordination, so that weak muscles may be strengthened and thus, deformity of the involved skeletal parts, avoided.[3] While this is not the place to discuss treatment of muscles, its importance must be emphasized (Plate V).

It has been our experience that such close observation of the symptoms and signs presented by muscle condition as we have indicated here permits a diagnosis of poliomyelitis in over 95% of the cases in the first five to seven days of the disease.

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BOOK REVIEWS

Water and Salt Depletion. *H. L. Marriott, C.B.E., M.D., F.R.C.P.* Springfield, Ill., Charles C. Thomas, 1950. 80 pp. 10 illus. $2.00.

This book by Dr. Marriott, who is one of the chief internists of the Middlessex Hospital in London, represents a very up-to-date account of water and salt depletion and of water or salt depletion. The distinction between the discrete water depletion, salt depletion, and mixed types is made very clear in this book. It is 80 pages long, with short chapters, and is very readable. The bibliography includes a large number of American references and reference is adequately made to the work of Gamble, Maddock and others.

Included are several charts and tables which are simple and lead to a proper understanding of the subject. The book can be recommended for complete reading by surgeons, both those in practice and those studying for the board examinations.

Epilepsy and Convulsive Disorders. *Edward M. Bridges, M.D.* New York, McGraw-Hill Company, 1949.

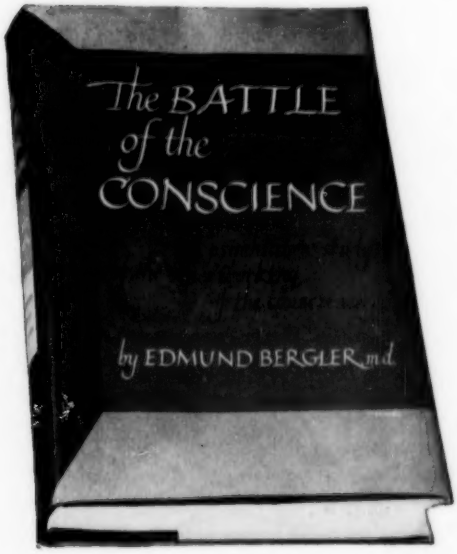
This monograph on the convulsive disorders in children brings all aspects of the subject to the clinical fore. The author evaluates each factor that bears on this complex problem as a basis for the effective management of the individual case. It involves the role of heredity, cerebral injury, intercurrent disease, diet, emotion, personality, the attitude of the patient, his family and his associates towards this type of disease. Each of these aspects of the problem is given due consideration for the total management of the affected child. Such an application displaces the prescription of an anticonvulsive drug as the routine procedure and offers instead a wholesome therapeutic armamentarium that will accrue to the developmental advantage of the child and the psychological responses of the parents. Each chapter is followed by a bibliography which is, unfortunately, duplicated alphabetically in the appendix. Since the book is intended for physicians as well as parents and social workers there is needless repetition. To appease parents more emphasis is given to everyday management than to more effective forms of treatment. Great stress is placed upon surgical treatment of convulsions arising from localized cerebral lesions. The book is well written, clearly illustrated and carefully documented. It is invaluable in the complete management of a child with any form of chronic convulsive disorder.—*I. Newton Kugelmass, M.D.*

The Strategy of Handling Children. Questions and Answers of Parents' Problems. *Donald A. Laird, Sc.D.* and *Eleanor C. Laird, Research Librarian.* New York, Funk & Wagnalls, 1949.

This popular edition of everyday problems of children is presented in question and answer form. The questions arose out of a series of lectures given by the authors and the answers were formulated for this textbook. The subject material is divided into several chapters, one devoted to Prenatal Problems, another to Growth and Development and a third to Individual Effectiveness. The authors give a timetable of growth and development at yearly intervals without any explanation of the normal variations that occur in individual children. The developmental achievements of a child observed by Gesell and his associates deviate considerably from the so-called norm or average. Parents take such tables literally unless such an explanation is given; they may even attempt to force the child into the mediocre mean without the realization that these body variations in form and function arise from internal forces of growth. It takes a harmonious integration of motivating elements to create the individual timetable of growth and development. There are a series of interesting questions of heredity clearly answered for the curious parent. The authors stress wisely that children come through parents rather than from them. The emotional problems of early infancy are given less consideration than those of later childhood. This is unfortunate because the entire personality structure is founded upon adequate emotional relationships ingrained in the early years of life. The authors tend to give general bits of wisdom in short, crisp sentences. Unfortunately, such general advice has multiple meanings. Each parent interprets such generalizations in his own way, hence such advice defeats its purpose. Some of the advice on mouth care is not in accord with current concepts. For example, gum-chewing, thumb-sucking and tooth-picks are condoned. Formidable advice is given on development of personality, personal hygiene, hygienic care, improvement of the senses, perfection of learning power, development of courage and formation of good habits. Each discussion is illustrated by personal instances in the lives of great men and women during childhood. The book is a fine collection of authentic answers to many of the questions asked by parents. The questions are always the same by parents of each generation but the answers differ in each era. The questions in this book are answered by psychologists from this standpoint. Obviously, solutions to children's problems are as much physical, mental and social as they are mental and psychologic. There is a tendency for some of the answers to be one-sided in consonance with the current psychological era.

The Battle of the Conscience

By
EDMUND BERGLER, M.D.



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